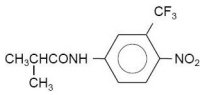
EULEXIN - flutamide capsule
Schering Corporation

WARNINGS

Hepatic Injury
There have been postmarketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.
Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, hyperbilirubinuria, jaundice, or right upper quadrant tenderness. If at any time a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

PRODUCT INFORMATION

DESCRIPTION
EULEXIN Capsules contain flutamide, an acetanilid, nonsteroidal, orally active antiandrogen having the chemical name, 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide.
Each capsule contains 125 mg flutamide, USP. The compound is a buff to yellow powder with a molecular weight of 276.2 and the following structural formula:



The inactive ingredients for EULEXIN Capsules include: corn starch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, and the following dye systems: FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, titanium dioxide, black ink, and other inactive ingredients.

CLINICAL PHARMACOLOGY

General
In animal studies, flutamide demonstrates potent antiandrogenic effects. It exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgen in target tissues or both. Prostatic carcinoma is known to be androgen-sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen, eg, castration. Elevations of plasma testosterone and estradiol levels have been noted following flutamide administration.

Pharmacokinetics

Absorption
Analysis of plasma, urine, and feces following a single oral 200 mg dose of tritium-labeled flutamide to human volunteers showed that the drug is rapidly and completely absorbed. Following a single 250 mg oral dose to normal adult volunteers, the biologically active alpha-hydroxylated metabolite reaches maximum plasma concentrations in about 2 hours, indicating that it is rapidly formed from flutamide. Food has no effect on the bioavailability of flutamide.

Distribution

In male rats administered an oral 5 mg/kg dose of ^{14}C-flutamide neither flutamide nor any of its metabolites is preferentially accumulated in any tissue except the prostate. Total drug levels were highest 6 hours after drug administration in all tissues. Levels declined at roughly similar rates to low levels at 18 hours. The major metabolite was present at higher concentrations than flutamide in all tissues studied. Following a single 250 mg oral dose to normal adult volunteers, low plasma concentrations of flutamide were detected. The plasma half-life for the alpha-hydroxylated metabolite of flutamide is approximately 6 hours. Flutamide, *in vivo*, at steady-state plasma concentrations of 24 to 78 ng/mL is 94% to 96% bound to plasma proteins. The active metabolite of flutamide, *in vivo*, at steady-state plasma concentrations of 1556 to 2284 ng/mL, is 92% to 94% bound to plasma proteins.

Metabolism
The composition of plasma radioactivity, following a single 200 mg oral dose of tritium-labeled flutamide to normal adult volunteers, showed that flutamide is rapidly and extensively metabolized, with flutamide comprising only 2.5% of plasma radioactivity 1 hour after administration. At least six metabolites have been identified in plasma. The major plasma metabolite is a biologically active alpha-hydroxylated derivative which accounts for 23% of the plasma tritium 1 hour after drug administration. The major urinary metabolite is 2-amino-5-nitro-4-(trifluoromethyl)phenol.

Excretion
Flutamide and its metabolites are excreted mainly in the urine with only 4.2% of a single dose excreted in the feces over 72 hours.

Plasma Pharmacokinetics of Flutamide and Hydroxyflutamide in Geriatric Volunteers (mean ± SD)				
	Single Dose		**Steady State**	
	Flutamide	**Hydroxyflutamide**	**Flutamide**	**Hydroxyflutamide**
C_{max} (ng/mL)	25.2 ± 34.2	894 ± 406	113 ± 213	1629 ± 586
Elimination half-life (hr)	—	8.1 ± 1.3	7.8	9.6 ± 2.5
T_{max} (hr)	1.9 ± 0.7	2.7 ± 1.0	1.3 ± 0.7	1.9 ± 0.6
C_{min} (ng/mL)	—	—	—	673 ± 316

Special Populations

Geriatric
Following multiple oral dosing of 250 mg t.i.d. in normal geriatric volunteers, flutamide and its active metabolite approached steady-state plasma levels (based on pharmacokinetic simulations) after the fourth flutamide dose. The half-life of the active metabolite in geriatric volunteers after a single flutamide dose is about 8 hours and at steady state in 9.6 hours.

Race
There are no known alterations in flutamide absorption, distribution, metabolism, or excretion due to race.

Renal Impairment
Following a single 250 mg dose of flutamide administered to subjects with chronic renal insufficiency, there appeared to be no correlation between creatinine clearance and either C_{max} or AUC of flutamide. Renal impairment did not have an effect on the C_{max} or AUC of the biologically active alpha-hydroxylated metabolite of flutamide. In subjects with creatinine clearance of <29 mL/min, the half-life of the active metabolite was slightly prolonged. Flutamide and its active metabolite were not well dialyzed. Dose adjustment in patients with chronic renal insufficiency is not warranted.

Hepatic Impairment
No information on the pharmacokinetics of flutamide in hepatic impairment is available (see **BOXED WARNING, Hepatic Injury**).

Women, Pediatrics
Flutamide has not been studied in women or pediatric subjects.

Drug-Drug Interactions
Interactions between EULEXIN Capsules and LHRH-agonists have not occurred. Increases in prothrombin time have been noted in patients receiving warfarin therapy (see **PRECAUTIONS**).

Clinical Studies
Flutamide has been demonstrated to interfere with testosterone at the cellular level. This can complement medical castration achieved with LHRH-agonists which suppresses testicular androgen production by inhibiting luteinizing hormone secretion.

The effects of combination therapy have been evaluated in two studies. One study evaluated the effects of flutamide and an LHRH-agonist as neoadjuvant therapy to radiation in stage B_2-C prostatic carcinoma and the other study evaluated flutamide and an LHRH-agonist as the sole therapy in stage D_2 prostatic carcinoma.

Stage B_2-C Prostatic Carcinoma
The effects of hormonal treatment combined with radiation was studied in 466 patients (231 EULEXIN + goserelin acetate implant + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B_2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of EULEXIN Capsules (250 mg t.i.d.) and goserelin acetate (3.6 mg depot) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years, P<0.001). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, P = 0.058). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, P<0.001). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, P<0.001).

Stage D_2 Prostatic Carcinoma

To study the effects of combination therapy in metastatic disease, 617 patients (311 leuprolide + flutamide, 306 leuprolide + placebo) with previously untreated advanced prostatic carcinoma were enrolled in a large multicentered, controlled clinical trial.

Three and one-half years after the study was initiated, median survival had been reached. The median actuarial survival time was 34.9 months for patients treated with leuprolide and flutamide versus 27.9 months for patients treated with leuprolide alone. This 7-month increment represents a 25% improvement in overall survival time with the flutamide therapy. Analysis of progression-free survival showed a 2.6-month improvement in patients who received leuprolide plus flutamide, a 19% increment over leuprolide and placebo.

INDICATIONS AND USAGE

EULEXIN Capsules are indicated for use in combination with LHRH agonists for the management of locally confined Stage B_2-C and Stage D_2 metastatic carcinoma of the prostate.

Stage B_2-C Prostatic Carcinoma

Treatment with EULEXIN Capsules and the goserelin acetate implant should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Stage D_2 Metastatic Carcinoma

To achieve benefit from treatment, EULEXIN Capsules should be initiated with the LHRH-agonist and continued until progression.

CONTRAINDICATIONS

EULEXIN Capsules are contraindicated in patients who are hypersensitive to flutamide or any component of this preparation.
EULEXIN Capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment).

WARNINGS

Hepatic Injury

SEE BOXED WARNING.

Use in Women

EULEXIN Capsules are for use **only** in men. This product has no indication for women, and should not be used in this population, particularly for nonserious or nonlife-threatening conditions.

Fetal Toxicity

Flutamide may cause fetal harm when administered to a pregnant woman (see **Pregnancy**).

Aniline Toxicity

One metabolite of flutamide is 4-nitro-3-fluoro-methylaniline. Several toxicities consistent with aniline exposure, including methemoglobinemia, hemolytic anemia, and cholestatic jaundice have been observed in both animals and humans after flutamide administration. In patients susceptible to aniline toxicity (eg, persons with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease, and smokers), monitoring of methemoglobin levels should be considered.

PRECAUTIONS

General

In clinical trials, gynecomastia occurred in 9% of patients receiving flutamide together with medical castration.

Information for Patients

Patients should be informed that EULEXIN Capsules and the drug used for medical castration should be administered concomitantly, and that they should not interrupt their dosing or stop taking these medications without consulting their physician.

Laboratory Tests
Regular assessment of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise significantly and consistently during EULEXIN therapy the patients should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment period free of antiandrogen while continuing the LHRH analogue may be considered.

Drug Interactions
Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide was initiated. Therefore, close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when EULEXIN Capsules are administered concomitantly with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 1-year dietary study in male rats, interstitial cell adenomas of the testes were present in 49% to 75% of all treated rats (daily doses of 10, 30, and 50 mg/kg/day were administered). These produced plasma C_{max} values that are 1-, 2- to 3-, and 4-fold, respectively, those associated with therapeutic doses in humans. In male rats similarly dosed for 1 year, tumors were still present after 1 year of a drug-free period, but the incidences were 43% to 47%. In a 2-year carcinogenicity study in male rats, daily administration of flutamide at these same doses produced testicular interstitial cell adenomas in 91% to 95% of all treated rats as opposed to 11% of untreated control rats. Mammary adenomas, adeno carcinomas, and fibroadenomas were increased in treated male rats at exposure levels that were 1- to 4-fold those observed during therapeutic dosing in humans. There are likewise reports of malignant breast neoplasms in men treated with EULEXIN Capsules (see **ADVERSE REACTIONS** section).
Flutamide did not demonstrate DNA modifying activity in the Ames *Salmonella*/microsome Mutagenesis Assay. Dominant lethal tests in rats were negative.
Reduced sperm counts were observed during a 6-week study of flutamide monotherapy in normal human volunteers.
Flutamide did not affect estrous cycles or interfere with the mating behavior of male and female rats when the drug was administered at 25 and 75 mg/kg/day prior to mating. Males treated with 150 mg/kg/day (30 times the minimum effective antiandrogenic dose) failed to mate; mating behavior returned to normal after dosing was stopped. Conception rates were decreased in all dosing groups. Suppression of spermatogenesis was observed in rats dosed for 52 weeks at approximately 3, 8, or 17 times the human dose and in dogs dosed for 78 weeks at 1.4, 2.3, and 3.7 times the human dose.

Animal Toxicology
Serious cardiac lesions were observed in 2/10 beagle dogs receiving 25 mg/kg/day for 78 weeks and 3/16 receiving 40 mg/kg/day for 2–4 years. These lesions, indicative of chronic injury and repair processes, included chronic myxomatous degeneration, intraatrial fibrosis, myocardial acidophilic degeneration, vasculitis, and perivasculitis. The doses at which these lesions occurred were associated with 2-hydroxyflutamide levels that were 1- to 12-fold greater than those observed in humans at therapeutic levels.

Pregnancy

Pregnancy Category D
There was decreased 24-hour survival in the offspring of pregnant rats treated with flutamide at doses of 30, 100, or 200 mg/kg/day (approximately 3, 9, and 19 times the human dose). A slight increase in minor variations in the development of the sternebrae and vertebrae was seen in fetuses of rats treated with two higher doses. Feminization of the male rats also occurred at the two higher dose levels. There was a decreased survival rate in the offspring of rabbits receiving the highest dose (15 mg/kg/day, equal to 1.4 times the human dose).

ADVERSE REACTIONS

Stage B_2-C Prostatic Carcinoma
Treatment with EULEXIN Capsules and the goserelin acetate implant did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing flutamide + goserelin acetate implant + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below.

Adverse Events During Acute Radiation Therapy (within first 90 days of radiation therapy)			**Adverse Events During Late Radiation Phase (after 90 days of radiation therapy)**		
	(n=231)	**(n=235)**		**(n=231)**	**(n=235)**
	Goserelin acetate implant + EULEXIN + Radiation	**Radiation Only**		**Goserelin acetate implant + EULEXIN + Radiation**	**Radiation Only**
	% All	**% All**		**% All**	**% All**
Rectum/ Large Bowel	80	76	Diarrhea	36	40
			Cystitis	16	16
Bladder	58	60	Rectal Bleeding	14	20

Skin	37	37	Proctitis	8	8
			Hematuria	7	12

Additional adverse event data were collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

Stage D_2 Metastatic Carcinoma

The following adverse experiences were reported during a multicenter clinical trial comparing flutamide + LHRH agonist versus placebo + LHRH agonist.

The most frequently reported (greater than 5%) adverse experiences during treatment with EULEXIN Capsules in combination with an LHRH agonist are listed in the table below. For comparison, adverse experiences seen with an LHRH agonist and placebo are also listed in the following table.

	(n=294)	**(n=285)**
	Flutamide + LHRH agonist	**Placebo + LHRH agonist**
	% All	**% All**
Hot Flashes	61	57
Loss of Libido	36	31
Impotence	33	29
Diarrhea	12	4
Nausea/Vomiting	11	10
Gynecomastia	9	11
Other	7	9
Other GI	6	4

As shown in the table, for both treatment groups, the most frequently occurring adverse experiences (hot flashes, impotence, loss of libido) were those known to be associated with low serum androgen levels and known to occur with LHRH agonists alone.

The only notable difference was the higher incidence of diarrhea in the flutamide + LHRH agonist group (12%), which was severe in 5% as opposed to the placebo + LHRH agonist (4%), which was severe in less than 1%.

In addition, the following adverse reactions were reported during treatment with flutamide + LHRH agonist.

Cardiovascular System: hypertension in 1% of patients.

Central Nervous System: CNS (drowsiness/confusion/depression/anxiety/nervousness) reactions occurred in 1% of patients.

Gastrointestinal System: anorexia 4%, and other GI disorders occurred in 6% of patients.

Hematopoietic System: anemia occurred in 6%, leukopenia in 3%, and thrombocytopenia in 1% of patients.

Liver and Biliary System: hepatitis and jaundice in less than 1% of patients.

Skin: irritation at the injection site and rash occurred in 3% of patients.

Other: edema occurred in 4%, genitourinary and neuromuscular symptoms in 2%, and pulmonary symptoms in less than 1% of patients.

In addition, the following spontaneous adverse experiences have been reported during the marketing of flutamide: hemolytic anemia, macrocytic anemia, methemoglobinemia, sulfhemoglobinemia, photosensitivity reactions (including erythema, ulceration, bullous eruptions, and epidermal necrolysis), and urine discoloration. The urine was noted to change to an amber or yellow-green appearance which can be attributed to the flutamide and/or its metabolites. Also reported were cholestatic jaundice, hepatic encephalopathy, and hepatic necrosis. The hepatic conditions were often reversible after discontinuing therapy; however, there have been reports of death following severe hepatic injury associated with use of flutamide.

Malignant breast neoplasms have occurred rarely in male patients being treated with EULEXIN Capsules.

Abnormal Laboratory Test Values

Laboratory abnormalities including elevated SGOT, SGPT, bilirubin values, SGGT, BUN, and serum creatinine have been reported.

OVERDOSAGE

In animal studies with flutamide alone, signs of overdose included hypoactivity, piloerection, slow respiration, ataxia, and/or lacrimation, anorexia, tranquilization, emesis, and methemoglobinemia.

Clinical trials have been conducted with flutamide in doses up to 1500 mg per day for periods up to 36 weeks with no serious adverse effects reported. Those adverse reactions reported included gynecomastia, breast tenderness, and some increases in SGOT. The single dose of flutamide ordinarily associated with symptoms of overdose or considered to be life threatening has not been established.

Flutamide is highly protein bound and is not cleared by hemodialysis. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. If vomiting does not occur spontaneously, it should be induced if the patient is alert. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The recommended dosage is 2 capsules 3 times a day at 8-hour intervals for a total daily dose of 750 mg.

HOW SUPPLIED

EULEXIN Capsules, 125 mg, are available as opaque, two-toned brown capsules, imprinted with "Schering 525". They are supplied as follows:

NDC 0085-0525-05 - Bottles of 500
NDC 0085-0525-03 - Unit Dose packages of 100 (10 × 10's)
NDC 0085-0525-06 - Bottles of 180

Store between 2° and 30°C (36° and 86°F).
Protect the Unit Dose packages from excessive moisture.

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Rev. 12/00
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B-16887692